EXHIBIT 6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 13 2005

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Peter O. Safir, Esq.
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, D.C. 20004-2401

Re: Docket No. 2005P-0127/CP1

Dear Mr. Safir:

This responds to your citizen petition dated March 31, 2005 (Petition), and your related comment dated June 10, 2005 (Comment), both submitted on behalf of Aventis Pharmaceuticals Inc. (Aventis), concerning the approval of abbreviated new drug applications (ANDAs) for leflunomide. Aventis holds the new drug application (NDA 20-905) for the reference listed drug (RLD) for leflunomide, which is marketed under the brand name Arava. Arava is commercially available in 10-milligram (mg) and 20-mg strengths. Aventis also distributes 100-mg tablets, not available in pharmacies, but available free to physicians in blister packs of three tablets.

In the Petition, you request that (1) if an ANDA applicant is not seeking approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets, the Food and Drug Administration (FDA or the Agency) require the applicant to perform in vivo bioequivalence testing to confirm that five of its 20-mg tablets are bioequivalent to one Arava 100-mg tablet, and (2) the Agency withhold final approval of any leflunomide ANDA that either (a) does not seek approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets or (b) does not establish in vivo bioequivalence between five 20-mg leflunomide tablets and one Arava 100-mg tablet.

For the reasons that follow, the Petition is denied. This decision is based on a review of the Petition and the comments submitted in response to it,[1] as well as other information available to the Agency. Generic leflunomide product lines that provide the 10-mg and/or 20-mg strengths that contain the same labeling as Arava are not compelled to also provide the 100-mg tablet. Moreover, a generic sponsor of a 20-mg leflunomide tablet who has demonstrated bioequivalence to Arava 20-mg tablets, is not also required to demonstrate bioequivalence of five of the 20-mg generic leflunomide product to one Arava 100-mg tablet.

[1] These include comments submitted by Kali Laboratories, Inc. (Kali), dated May 12, 2005 (2005P-0127/C1), comments submitted by Olsson, Frank and Weeda, P.C., dated May 18, 2005 (2005P-0127/C2), and your Comment referenced above (2005P-0127/RC1).

2005P-0127

PDN 1

I. BACKGROUND

A. Factual Information

Leflunomide (Arava) is a pyridimine synthesis inhibitor that is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms and to retard structural damage. Leflunomide is metabolized to one primary active metabolite (M1) that is responsible for essentially all of its in vivo activity. M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. M1 has a half-life of 15 days. The usual daily dose of leflunomide is 20 mg. Because of the long half-life of M1, however, a loading dose of 100 mg per day for 3 days is recommended in Arava's approved labeling to quickly reach steady state plasma concentrations of M1. The use of a loading dose is not essential to the effective use of the product, and elimination of the loading dose may decrease the risk of adverse events.[2]

Bioequivalence between five 20-mg tablets and one 100-mg tablet of Arava has not been established. Arava 100-mg tablets have a formulation that is not proportionally similar relative to either the 20-mg or the 10-mg tablets.[3] FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book) lists both the 20-mg and the 100-mg tablets of Arava as the reference listed drugs (RLDs) for leflunomide tablets. FDA would not waive the requirement for the submission of evidence measuring the in vivo bioequivalence of five 20-mg leflunomide tablets (or ten 10-

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[2] The *DOSAGE AND ADMINISTRATION* portion of Arava's labeling states in part the following:

> **Loading Dose**
> Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.
> Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past (see **WARNINGS — Hepatotoxicity**).

Loading dose is also referred to in the following portion of the labeling:

> **Absorption**
> Following oral administration, peak levels of the active metabolite, M1, occurred between 6 - 12 hours after dosing. Due to the very long half-life of M1 (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of M1. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional.

[3] The 20-mg and 10-mg tablets are proportionally similar (see NDA 20905, Clinical Pharmacology and Biopharmaceutics Review(s) (attached at Tab 2 to the Petition) at 3). The 100-mg and 20-mg tablets are not proportionally similar (see Leflunomide Tablets, NDA Amendment/Biopharmaceutical Information, NDA #20-[90]5, enclosed with letter dated June 23, 1998, from Quintiles to Sandra Cook, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, FDA (attached at Tab 3 to the Petition) at 10). For a detailed definition of *dose proportionality*, see p. 11 of the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. Proportionality and nonproportionality of dosage strengths are important when considering bioequivalence requirements (e.g., when granting waivers of in vivo bioequivalence studies for a lower strength or strengths of a drug product).

mg tablets) and a 100-mg tablet if an ANDA applicant proposed to recommend using five 20-mg tablets (or ten 10-mg tablets) instead of a 100-mg tablet for the loading dose.

Arava was approved on September 10, 1998, at 10-mg, 20-mg, and 100-mg strengths.[4] As a new chemical entity, Arava had 5-year exclusivity under section 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355 (j)(5)(F)(ii)), during which time no generic applications could be submitted.[5] Because FDA determined under section 505A of the Act that Arava was entitled to pediatric exclusivity, the period of exclusive marketing was extended 6 months (i.e., until March 10, 2004).[6]

In January 2002, in a letter to pharmaceutical buyers, Aventis announced its decision "to discontinue [the] 100 mg Arava® (leflunomide) tablets trade package."[7] As your Comment acknowledges, Aventis no longer *sells* the 100-mg strength of the product (Comment at 2). Aventis does, however, continue to make the 100-mg product available free to physicians (*Id.*).[8] As acknowledged in comments submitted to the docket, generic drug applicants seek approval of the 10-mg and 20-mg strengths of leflunomide.

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[4] In 2002, in a citizen petition, Public Citizen asked the Agency to remove Arava from the market, based on the claim that its adverse events compared unfavorably with older treatments for rheumatoid arthritis. In 2003, an advisory committee meeting was held to consider the safety of the product. On March 23, 2004, in a formal response to the 2002 citizen petition, FDA announced that it continues to regard the product as safe (see Docket No. 2002P-0139/CP1).

[5] Arava also had 5-year exclusivity under section 505(c)(3)(E)(ii) of the Act. The Act's 5-year exclusivity provisions state that no ANDA (or new drug application under section 505(b)(2) of the Act (505(b)(2) application)) that references an NDA with such exclusivity can be submitted to FDA for 5 years after the date of approval of the NDA, except that an ANDA (or 505(b)(2) application) can be submitted 4 years after the date of the NDA's approval if it contains a certification stating that one or more patents claiming the drug described in the NDA, or use thereof, is invalid or not infringed (a paragraph IV certification) (see sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act). Such patents are listed in the Orange Book. Although a patent had been previously listed in the Orange Book for Arava, no patents were listed for Arava on or after the fourth anniversary of its approval, and no paragraph IV certifications were submitted in any ANDA for a generic leflunomide product. Accordingly, Arava enjoyed the full 5-year period of marketing exclusivity afforded by sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act.

[6] Your Petition was submitted approximately one year after this date. One commenter notes (see 2005P-0127/C1 at 1) that this would be at the end of the normal ANDA review cycle for an ANDA submitted on or near the date ANDAs were first eligible for submission, suggesting that the Petition intends (at least in part) to delay generic competition. We also note that the majority of the citations in your Petition are many years old, and were available to Aventis well before the petition was submitted.

[7] See http://www.aventis.custservices.com/news.asp?up=103. For a brief time FDA listed the 100-mg Arava product in the *Discontinued Drug Product List* of the Orange Book, but it is now listed again in the Orange Book's main *Prescription Drug Product List*.

[8] See also http://www.arava.com/professional/about_arava/initiation.do?warning=1.

B. Relevant Statutory Background

1. Summary of Approval Process

Under the Act, sponsors seeking to market innovator drugs must first obtain FDA approval by filing an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug (see sections 505(a) and (b) of the Act). The NDA applicant is also required to submit certain patent information to FDA; the Agency publishes patent information for approved drugs in the Orange Book.

The Act permits applicants to submit ANDAs for approval of generic versions of approved drug products (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug (see *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990)). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585. As mentioned above, by operation of the exclusivity protections afforded under the Act, ANDAs for leflunomide were not eligible for submission until March 10, 2004.

2. Summary of Statutory and Regulatory Standards

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent[9] to the RLD (see 21 U.S.C. 355(j)(2)(A)(iv)). When there are multiple strengths of a product, this refers to bioequivalence between the same strength of the ANDA product and the RLD.[10,11] There is no requirement for an ANDA sponsor to

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[9] Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

[10] The preamble to our 1992 final rule on ANDAs explains that, "In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug" (*Abbreviated New Drug Application Regulations*; Final Rule, 57 FR 17950, April 28, 1992).

[11] Often the showing of bioequivalence can be accomplished without the submission of an in vivo study. FDA's regulations describe when FDA may waive in vivo bioequivalence studies on different strengths of a drug in the same dosage form:

> The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

demonstrate equivalence between different strengths of its own product line.[12] Assuming that the other requirements applicable to ANDAs (which are not at issue here) are satisfied, FDA must approve the ANDA unless the information submitted in the ANDA is insufficient to show that the generic drug is bioequivalent to the RLD (see 21 U.S.C. 355(j)(4)(F)).

The Act also requires an ANDA applicant to provide, among other things, information to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, except for changes required because of differences approved under an ANDA suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers (see 21 U.S.C. 355(j)(2)(A)(v)). Examples of these changes are listed at 21 CFR 314.94(a)(8)(iv), although this list is not exhaustive.[13] Differences in labeling that may result because a generic drug and the RLD are produced or distributed by different manufacturers include, but are not limited to, differences in the labeled name, address, and phone number for the drug manufacturer; differences in labeled colors; differences in the labeled indications for the drug (e.g., if the RLD had existing exclusivity for a particular indication); and differences in the drug's labeled strengths (e.g., if a generic manufacturer does not seek approval for all strengths approved for the RLD) (this point is discussed further in section II below).

II. DISCUSSION

You believe that FDA has accepted ANDAs seeking to market 10-mg and 20-mg tablets but not 100-mg tablets of leflunomide. You claim that the products described in these ANDAs would have no 100-mg tablets to refer to in their labeling (Petition at 2). You maintain that the approved labeling for Arava contains important dosage and administration information regarding a 100-mg loading dose and that leflunomide ANDAs must likewise contain such labeling (Petition at 4-5). You assert that this information is not the type of information that can be omitted from ANDA labeling simply because the reference drug and the ANDA drug are

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(i) The bioavailability of this other drug product has been measured;
(ii) Both drug products meet an appropriate in vitro test approved by FDA; and
(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(21 CFR 320.22(d)(2)).

[12] Both the Act and the bioequivalence regulations (see 21 CFR Part 320) refer only to bioequivalence between the subject of the ANDA and the RLD.

[13] See, e.g., February 15, 2002, response to Donald O. Beers, David E. Korn, William J. McNichol, Marc J. Scheineson, and Tracy Zurzolo Frisch regarding Docket Nos. 00P-1550/CP1 & PSA1 and 01P-0428/CP1 & PSA1 concerning generic cefuroxime axetil products, at 18 ("The plain language of § 314.94(a)(8)(iv) explicitly recognizes that these differences listed in the regulation are examples; therefore, § 314.94(a)(8)(iv) recognizes that there are other differences in labeling between generic drug products and reference listed drugs that are permissible due to the fact that the generic drug product and reference listed drug product are produced or distributed by different manufacturers").

produced or distributed by different manufacturers and the ANDA manufacturer does not make a 100-mg tablet (Petition at 3 and Comment at 3). Finally, you claim that omission of the loading dose information may render the generics less effective than Arava (Petition at 3 and Comment at 3).

Your argument seems to be based on a false premise, namely, that if a particular generic manufacturer recommends in leflunomide labeling a loading dose of 100 mg for three days (3 x 100 mg), the manufacturer either must (1) provide its own 100-mg product or (2) recommend using five of its 20-mg tablets. You incorrectly speculate that generic sponsors will attempt to either replace the 100-mg tablet loading dose with a loading dose of five 20-mg tablets or remove mention of the loading dose from the label (Petition at 3). In the rest of the Petition, as well as in your Comment, you argue that replacing the 100-mg loading dose with a loading dose of five 20-mg tablets should require an in vivo bioequivalence study, and that it is legally and medically inappropriate to remove mention of the loading dose from the label. You seem to ignore a third possibility: that the labeling for a generic leflunomide product can recommend a loading dose of 3 x 100 mg that can be accomplished by the use of an approved 100-mg tablet from a different manufacturer. Given the unusual manner in which the 100-mg tablet for the loading dose has been distributed by Aventis (i.e., in blister packs of 3, for free and only to, and at the request of, a physician) and the fact there are circumstances when a loading dose should perhaps not be used, we do not find it unreasonable for a generic manufacturer to elect to market only the other dosage strengths.

A generic sponsor that markets only 20-mg and 10-mg leflunomide tablets must have the same labeling as the RLD, except for differences that would be permitted under 21 U.S.C. 355(j)(2)(A)(v), discussed in subsection I.B.2 above. As does the approved labeling for Arava (see footnote 2, *supra*), approved labeling for generic leflunomide products would include the recommendation of using 100-mg tablets for the loading dose. The 100-mg tablets could be either 100-mg Arava tablets or 100-mg generic tablets from a different sponsor that have been demonstrated to be bioequivalent to the 100-mg Arava tablets.[14] We agree that changes in labeling resulting from a difference in manufacturers must not render the proposed generic drug product less safe or effective than the RLD. But we do not see this as an issue here, for we do not intend to permit the labeling regarding use of a 100-mg tablet for the loading dose to be omitted, as you surmise (see Petition at 3 and 5); nor do we see that any change not permitted by the Act is needed in this labeling if a generic manufacturer chooses to market only the 20-mg and 10-mg strengths of leflunomide.

Labeling for generic leflunomide products approved in 10- and 20-mg strengths may reference a 100-mg leflunomide tablet that the generic sponsor does not produce. As reflected by existing precedents, ANDA sponsors may refer in their labeling to products they do not manufacture. For example, the product labeling for the anti-retroviral drug Videx (didanosine) delayed-release capsules makes reference to the package inserts for Videx chewable/dispersible tablets and

[14] Your Comment acknowledges that an ANDA applicant that seeks approval of a 20-mg leflunomide tablet, but not a 100-mg tablet, could propose to "reference [in the drug's label] a 100 mg tablet that the generic does not manufacture" (Comment at 3). You go on to assert that this option should not be permitted (*Id.*); however, you provide no explanation for your assertion, and, for the reasons discussed in the text above, we see no reasoned basis to accept it.

Videx pediatric powder for oral solution for information regarding the pediatric dose. Currently, the only approved generic didanosine (Barr ANDA 77-167) is for a delayed-release capsule, which has labeling that makes reference to the other Videx dosage forms, even though Barr does not itself provide these other dosage forms. It is also not uncommon for brand name products to refer in their labeling to other drugs that are not provided by the sponsor of the brand name product (e.g., the labeling of Oncaspar, an Aventis product, recommends its use in combination with the following products not made by Aventis: vincristine, methotrexate, cytarabine, daunorubicin, and doxorubicin; also, the labeling of Eloxatin, owned by Sanofi-Synthelabo, Inc., recommends that it be used in combination with infusional 5-FU/LV[5-fluorouracil/leucovorin], which Sanofi-Synthelabo, Inc., does not supply).

Additionally, there is nothing in the Act or the regulations that requires an ANDA applicant to seek approval for all available strengths of the RLD. Both the Act and the regulations state that the generic product must be the same strength (singular) as the listed drug (see 21 U.S.C. 355(j)(2)(A)(iii) and 21 CFR 314.92 and 314.94(a)(6)(i)), implying that each strength of a reference product is in some regards a separate listed drug (see footnote 10, *supra*). It is not unusual for an ANDA applicant to decline to seek approval for certain strengths approved for the RLD (see the June 11, 2002, response in Docket Nos. 01P-0495, 02P-0191, and 02P-0252, in which FDA permitted ANDAs for tramadol that do not provide a low dose for titration that is provided by the manufacturer of the RLD). The following products are all examples from the Orange Book (2004 printed edition) in which at least one generic manufacturer has omitted at least one strength of the RLD: alprazolam tablets, amitriptyline hydrochloride tablets, haloperidol tablets, hydralazine hydrochloride tablets, hydrochlorothiazide tablets, meclizine hydrochloride tablets, mirtazapine orally disintegrating tablets, nefazadone hydrochloride tablets, nifedipine capsules, nitrofurantoin (macrocrystaline) capsules, propranolol hydrochloride tablets, trazadone hydrochloride tablets, and thioridazine hydrochloride tablets.[15] It should be noted that the reverse may also be true (i.e., the reference product may not provide strengths that a generic applicant provides (e.g., methyldopa tablets, propranolol hydrochloride tablets)).

In light of the discussion above, FDA will require the labeling for generic leflunomide products to include the labeling approved for the RLD, Arava, concerning the use of a 100-mg loading dose. Thus, your concern that (1) this labeling will be omitted for generic leflunomide products that are approved at only 10-mg and 20-mg strengths, or (2) the labeling will be changed to recommend the use of five 20-mg tablets instead of a 100-mg tablet absent appropriate bioequivalence data, is unfounded.

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[15] You state in your Comment that another example cited by Kali in its comments on the Petition (2005P-0127/C1), oxycodone hydrochloride extended release (ER) tablets, "is inapposite" because dose proportionality and/or bioavailability were established for each strength of the RLD (Comment at 3). You note that, in the case of leflunomide, dose proportionality has not been established for all of the RLD's approved strengths (*Id.*). However, while, as you acknowledge, the labeling for the generic oxycodone hydrochloride ER product includes (as does the labeling for its RLD) a statement asserting that dose proportionality and/or bioavailability have been established for all available strengths at which the RLD is approved, there is no such claim in the approved labeling for Arava. Therefore, an applicant seeking approval for generic leflunomide tablets need not establish dose proportionality for all of Arava's approved strengths; nor, as explained above, must it demonstrate bioequivalence of five 20-mg generic leflunomide tablets (or ten 10-mg tablets) to one Arava 100-mg tablet.

III. CONCLUSION

It is not necessary for a generic leflunomide sponsor to either produce a 100-mg tablet or demonstrate bioequivalence of five 20-mg tablets to one 100-mg Arava tablet. A generic leflunomide product that refers in its labeling to a 100-mg tablet (which is available from Aventis) as the loading dose will be appropriately labeled with respect to the loading dose. For these reasons your Petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research